QUANTUM CHEMICAL, SPECTROSCOPIC, ELECTRONIC INVESTIGATIONS AND MOLECULAR DOCKING STUDIES ON SELECTED COMPOUNDS OF BIOLOGICAL IMPORTANCE

A SYNOPSIS

Submitted by

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(Reg. No. 201915141)

in partial fulfillment for the award of the degree of

DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSICS

SCHOOL OF ADVANCED SCIENCES

KALASALINGAM ACADEMY OF RESEARCH AND EDUCATION

(DEEMED TO BE UNIVERSITY)

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TAMIL NADU, INDIA

JULY 2022

1. INTRODUCTION

Organic compounds are large class of chemical compounds in which one or more atoms of carbon are covalently linked to atoms of other elements, most commonly hydrogen, oxygen, or nitrogen. They are a class of important biomolecules with numerous biological and pharmaceutical applications. Most of the drugs found in nature or synthesized in the laboratory are done by using organic compounds. Due to their small size, they can bind with protein receptors or enzymes and inhibit their functions, thus showing drug equality. The binding of the molecules to the receptor depends upon the types of chemical bonds and hydrophobic interactions [1]. Vibrational (infrared and Raman) spectroscopy has been playing a very important role in the identification of functional groups. Recent rapid development in vibrational spectroscopy has greatly encouraged its application to analytical chemistry, pharmaceutical industry, tissue research, biomedical research and applications, forensic science, diagnostics and environmental sciences [2,3].

Further, the quantum mechanical (QM) computational tools have significant advancement for interpreting the frequency assignments. The systematic inaccuracies of the calculated values are rectified in the scaled quantum mechanical (SQM) technique by a scale factor in chemically related molecules [4]. Since for the past few years, density functional theory (DFT) has appeared as a potential QM method which is satisfactorily meticulous as well as competent to be employed in pharmaceutical studies. DFT study has been accepted as a popular post- Hartree Fock (HF) approach for the computation of molecular structure, vibrational wave numbers and energies of molecules [5] for their efficiency and accuracy with respect to the evaluation of a number of molecular properties. The present implementation of DFT theory using GAUSSIAN 09W program provides a flexible and powerful toolbox for theoretical modelling [6]. In DFT approaches, Becke's three-parameter hybrid function associated with the Lee-Yang - Parr relationship (B3LYP) expects good calculation for structural analysis [7] and improves electron correlation theory [8,9]. In this study, the B3LYP/6-311++G(d,p) basis set [10] and cc-pVTZ basis set [11] has been used for improved efficiency of polar bonds of C groups and to carry out more functions per atom. cc-pVTZ basis set is a dunning's correlation consistent basis set which has redundant function removed in order to increase computational efficiency. Further, Molecular docking (MD) has been used in the drug development to provide possible protein-ligand interactions [12]. Hence, in the present study, the vibrational spectra

and quantum computational studies have been carried out for potential bioactive agents.

2. LITERATURE REVIEW

The reviews of literature for the selected biomolecules in this study are detailed as follows:

2.1. 1-aminohomopiperidine

Piperidine is a heterocyclic family comprising of a six-membered ring that includes five methylene groups (-CH2-) and one amine gather (-NH-). It is a main part in the different drugs which are of significant interest. It is additionally of prime significance in a few chemical degradation responses, for illustration, DNA sequencing in altered nucleotides cleavage. Recent years, piperidine frameworks have moved into preclinical challenging [13]. It shows numerous biological actions viz. a few of the piperidine-covering structures established farnesyl transferase (FT) inhibition, an enzyme that's found to be dynamic in different types of cancer [14]. Recently, many reports based on piperidine derivatives showed biological efficacy and solid inhibition activity against breast cancer marker [15,16]. These innumerable applications of piperidine derivatives were motivated for the theoretical and experimental investigations on the 1-aminohomopiperidine (1AHP). From literature report, no computation study has been done on 1AHP molecule as a powerful drug application. In this study, the structural and vibrational wavenumbers, molecular geometries and molecular orbital energies of 1AHP has been computed utilizing DFT/B3LYP/6-311++G(d,p) basis set. Further, the MD investigation has been carried out to confirm the repressive nature of 1AHP against breast cancer related proteins.

2.2. 2,5-diphenyl furan

Furan is typical aromatic hetero cyclic compound which contains a diphenyl ring and an oxygen atom. Furan found in natural plants, many processed foods, beverages counterfeit medicines with highly stable chemical structure. The main source of furan has been obtained from the thermally degradation of amino acids and carbohydrates. Recent studies on furan and its derivatives pose many antivirals, antifungal, antibacterial, antitumorigenic, anti-inflammatory, antifertility, hypo glycemic and cytostatic properties [17,18]. The day-by-day advancement on heterocyclic chemistry leads to deep interest to the researchers to develop new drugs. From the literature report, no computation study has been done on 2,5-diphenyl furan (DPF) molecule as a powerful drug application [19,20]. In this study, the structural

and electronic excited states related to stability and reactivity of DPF has been computed with DFT/B3LYP/6-311++G(d,p) technique. From the MD analysis [21], the binding scores of the receptors are found more efficient against SARS-CoV-2 M^{pro} which provide pathway to enhancement in clinical diagnoses.

2.3. 3,3,5,5-tetramethyl-2-pyrrolidone

The pyrrolidine has five-membered ring with nitrogen widely used by medicinal purposes to cure human diseases. Recently, many studies provide to determine the suitable structure of pyrrolidone and its derivatives using the density functional theory (DFT) at B3LYP method [22,23]. Recently, pyrrolidine/thioxothiazolidin-4-one derivatives have been studied by DFT, docking and antimicrobial calculations [24]. Similarly, the synthesis, acid dissociation constant, drug-likeness for polysubstituted pyrrolidines have been investigated by experimental and density functional theory study [25]. From the literature data, no computation study has been done on 3,3,5,5-tetramethyl-2-pyrrolidone (TM-2-P) in the drug usage. In present work, the optimized structure of TM-2-P has been analyzed, which enables the potential breakthrough in the drug development based on molecular docking study. Also, the nucleophilic and electrophilic regions of the molecule, frontier orbital energies, Mullikan charges, intermolecular interactions of TM-2-P have been calculated with DFT/B3LYP/ 6-311+G(d,p) method. The molecular docking study is utilized effectively to find the efficient inhibitor for TM-2-P. The binding affinities and other different interactions that are associated between the various amino acid residues and ligands have been examined.

2.4. p-(2-bromoethoxy) anisole

Anisole derivatives have more electrons than benzene because of the resonance effect of the methoxy group on the aromatic ring. They are utilized in fragrance and chemical synthesis. Owing to their important effects, i.e. back-donation and conjugation, they can be good and influencing the electronic characteristics of the system. They are also utilized in the pharmaceutical's fields. Particularly, in the treatment of breast cancer which is measured to be the fastest malignancy [26]. They show strong inhibition activity which are mostly used as a targeted protein for drug designing [27]. Further, many studies on the structures of anisole derivatives were carried out by DFT computation [28,29]. The interactions of anisole and thioanisole derivatives with gold clusters have been studied by DFT calculations [30]. Similarly, the DFT based mechanism of hydrodeoxygenation in anisole decomposition over

metal loaded acids has been investigated [31]. Recently, the DFT investigation of role of N–H···O and N–H···π interactions in the stabilization of the hydrogen bonded complexes of anisole with aromatic amines has been established [32]. In the literature report, no theoretical and computational (DFT-B3LYP/6-311++G(d,p) studies on p-(2-bromoethoxy) anisole (2BEA) in drug plan. Accordingly, in this work, the geometrical parameters, IR and Raman vibrational intensities and orbital molecular energies of 2BEA are calculated by the B3LYP/6-311++G(d,p) basis set.

2.5. 4,7-dihydroxycoumarin and 7-methoxy coumarin

Coumarins are benzopyrone family with a wide distribution in nature. It has a characteristic benzopyrone structure and plays a significant role in naturally arising or manufactured oxygen-containing heterocycles [33]. The heterocyclic oxygen-containing structure of coumarin makes them useful as antioxidant, anticoagulant, antiviral, antimicrobial, antiparasitic, antifungal, anti-diabetic, anticancer, anti-neurodegenerative, analgesic, and anti-inflammatory agents [34,35]. A good number of reviews appear in literature which summarize and highlight the advanced applications of coumarins, where their anti-cancer and anti-oxidant properties are important [36]. Moreover, vitamin K opponents, such as warfarin and acenocoumarol, are synthetic 4-hydroxycoumarin based drugs used to treat blood coagulation [37]. In sunscreen formulations, a naturally occurring 7-hydroxycoumarin is utilized as an active component [38]. Kostova *et al*. stated that the complexes of 4-methyl-7-hydroxycoumarin lanthanide and ligand or transition metal ions show promise in cytotoxic activities equivalent to vitamin C and quercetin [39,40]. Due to their versatility, the coumarin derivatives have been used in the pharmaceutical industry as antibiotics, antiviral, antimicrobial and anticoagulants agents and as pH indicators in biological systems and medical sciences [41-46]. These innumerable applications of hydroxy and methoxy coumarins have been motivated for the theoretical DFT/B3LYP/cc-pVTZ method of calculations and experimental investigations on 4,7-dihydroxycoumarin (DHC) and 7-methoxy coumarin (7MC).

3. OBJECTIVES

Biological and pharmaceutical active compounds are purchased from chemical company and these samples were used to record the FT-IR and FT-Raman spectrum measurements. The vibrational spectroscopic characterizations are used for the interpretation of molecular vibrations and to confirm the functional groups of the molecules. The computational studies such as minimum energy, molecular geometry

optimizations, thermodynamical properties, vibrational frequency calculations, IR intensity, Raman activity and the force field calculations are done by using GAUSSIAN 09W program exploiting B3LYP functional accompanied with the standard B3LYP basis sets. Initially, the molecular structures were optimized, and after that the vibrational wavenumbers, other molecular properties such as highest occupied and lowest unoccupied molecular orbitals (HOMO-LUMO) [47], Molecular electrostatic potential (MEP) [48], Mulliken charge (MC) [49], Nuclear Magnetic Resonance [50] (^{13}C NMR, ^{1}H NMR), Ultraviolet visible (UV-vis) [51] spectroscopic studies, Natural bond orbital (NBO) [52] analysis have been calculated. SQM method ensures the enhanced assertion between the experimental and DFT computed values. The MOLVIB Program (Adaptation V7.0-G77) by Sundius [53] and VEDA 4.0 program [54] are used in the calculation of the potential energy distribution (PED) for distinctive vibrational modes. MD method is one of the computational software techniques and it is a boon for new drug discovery and advanced pharmaceutical research. The structure of proteins was taken from Protein Information Bank (http://www.pdb.org) [55]. The molecules have been taken as ligands, and their structures were gotten from the open ligand databases: PubChem (http://pubchem.ncbi.nlm.nih.gov) [56]. Discovery Studio (Adaptation: 2017 R2 client) [57] program have been utilized to assess the protein structure and amino corrosive location by docking interaction with the molecules. MD is performed by Auto Dock Vina (Adaptation: 4.2.1) [58]. In vitro cytotoxicity analysis (MTT-3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide) has been used to check the anti-cancer activity of molecules [59]. Using the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity)-SAR prediction tool [60], the toxicity of the systems has been assessed. These mentioned properties of the selected molecules can be used in various pharmaceutical activities.

4. RESEARCH GAP

Diseases like cancer, diabetes, autoimmunity, cardiovascular and neurodegenerative disorders are caused in human body due to oxidative stress produced by free radicals or unpaired electrons. These are responsible for affecting the biomolecules such as DNA, proteins, enzymes and lipids leading to oxidative stress and molecular damage of cells and tissues. Extensive research is being carried out in identification of new antioxidants to restrict the deleterious character of free radicals by radical scavenging activity. Hence, new effective biological properties of

selected molecules are needed for their various biological and pharmaceutical applications.

Among the computational techniques, DFT method is a significant one to increase the computational accuracy without the additional increase in computing time. Modern drug discovery is based on molecular modelling techniques. This molecular docking method drastically minimize the time in analyzing and identifying new and effective drugs with minimum side effects. Hence, the docking computations are used to analyses the mode of interaction either by intercalation or groove binding ability between DNA and molecules. The simulations obtained from molecular docking are used to determine the inhibition between the ligand and receptor by exploring their binding modes and interaction at the active site of the proteins. The binding modes, docking scores and binding energies are obtained from the results. Therefore, the present work has been carried out to understand the complete information about the biological properties of the molecules.

5. ORGANIZATION OF THESIS

The thesis comprises of **NINE** chapters.

Chapter 1

Chapter one deals with the spectroscopy techniques such as FT-IR, FT-Raman, UV-Vis and NMR. The theoretical methods used for quantum chemical computations are briefly described.

Chapter 2

In chapter two, the reviews of literature for the selected biomolecules in this study are detailed.

Chapter 3

In the chapter three, the detailed frequency analyses, molecular stability interactions and charge exchanges of 1-aminohomopiperidine (1AHP) have been discussed with B3LYP/6-311++G(d,p) calculations. Frontier molecular orbital analysis, NBO, NMR, MEP, MC analysis and the UV absorption have also been studied by using DFT method. The molecular docking studies of the molecule with ERα are explained for its breast cancer efficacy. Furthermore, in silico ADMET results exhibited a low LD50 value and all the above results are discussed in the chapter 3.

Chapter 4

In chapter four, the vibrational frequencies and DFT/B3LYP/6-311++G(d,p) studies of 2,5-diphenyl furan (DPF) has been carried out. From the estimation, HOMO-LUMO energy gap clearly significant the charge transfer occurs within the molecule. The intra molecular interaction and delocalization of the charges has been studied using NBO analysis. In addition, electrostatic potential, NMR, UV, MC calculations are also performed. The docking investigation has been carried out to confirm the repressive nature of molecule against SARS-CoV-2 main protease (M^{pro}) proteins. Also, in silico ADMET studies has been evaluated for the DPF to estimate its drug likeness and these outcomes are detailed in the chapter 4.

Chapter 5

In chapter five, the work focused on 3,3,5,5-tetramethyl-2-pyrrolidone (TM-2-P) to be a potential candidate for breast cancer diagnosis. The DFT/B3LYP B3LYP/ 6-311+G(d,p) method is used to predict the molecular geometries, vibrational assignments, NMR, MC and electronic properties. The chemical reactivity of molecule has been studied using the frontier orbital analysis. The molecular interaction is calculated by using the electrostatic potential maps. The docking calculation and ADMET analysis have been performed to obtain the biochemical activities of the TM-2-P against the breast cancer and these results are the subject matter of chapter 5.

Chapter 6

Chapter six is concerned with the vibrational spectra of p-(2-bromoethoxy) anisole (2BEA) with DFT/B3LYP/6-311++G(d,p) basis set. The molecular geometry, MEP, Mulliken charge, NBO, NMR, UV analysis and thermodynamic limits have been detailed. Furthermore, the molecular docking results exposed the molecular interaction with breast cancer marker (ERα). In silico ADMET properties such as LD50 has also been analyzed for the molecule to estimate its drug likeness and the above outcomes are discussed in chapter 6.

Chapter 7

In the seventh chapter, the quantum chemical studies of 4,7-dihydroxycoumarin (DHC) have been performed using the cc-pVTZ level of basis set. The DHC molecular structure has been optimized and the computed frequency assignments have been correlated well with the experimental results. The experimental ^{13}C NMR shifts of DHC have been compared with the computed ^{13}C NMR and are detailed. In

addition, HOMO-LUMO, electrostatic potential, NBO, UV and MC calculations are also performed. According to in vitro cytotoxicity studies, the DHC compound has a cytotoxic impact on the Michigan Cancer foundation-7 (MCF-7) breast cancer cell line. The docking study and ADMET analysis approves that the DHC works as a new inhibitor of breast cancer targeted proteins such as EGFR, ERα, and all the above are detailed in chapter 7.

Chapter 8

In the chapter 8, the vibrational assignments of 7-methoxycoumarin (7MC), a potential anticancer agent, have been discussed by the experimental (FT-IR and FT-Raman) and theoretical methods. The density functional theory DFT-B3LYP technique with cc-pVTZ basis set is utilized to examine the molecular geometry. The NBO analysis, HOMO-LUMO transition and the UV absorption, NMR and MC by using DFT approach have been investigated. The docking studies have been executed for interaction of 7MC with the sites of human Bruton's tyrosine kinase (BTK) (Figure 1(a)), Phosphoinositide 3'-kinase (PI3K) (Figure 1(b)) and Spleen Associated Tyrosine Kinase (SYK) (Figure 1(c)). Further, MTT assay is used to study the anticancer activity of 7MC through five human cancer cell lines (A-549, HEPG2, HEp2, MCF-7, and HL-60) (Figure 2). In addition, ADMET studies have also been investigated for 7MC and the results are discussed in chapter 8.

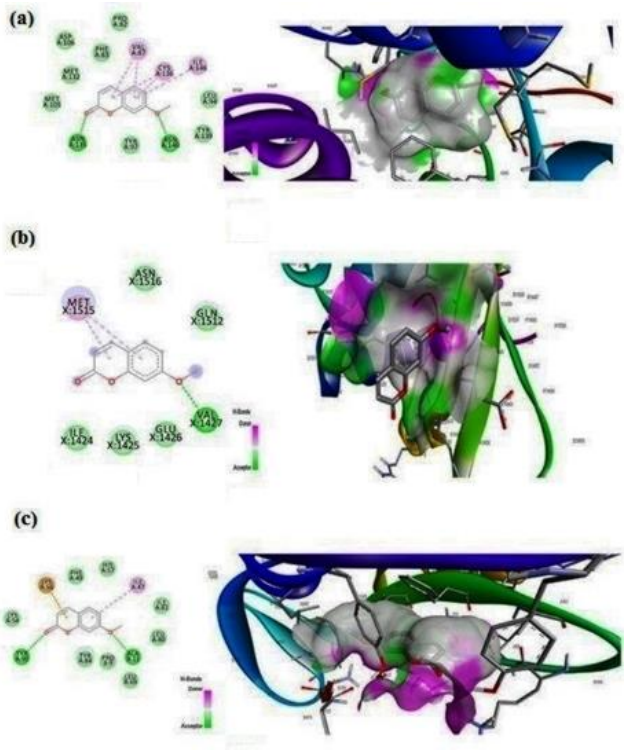

Figure 1: Interaction of 7-methoxycoumarin with (a) BTK, (b) PI3K and (c) SYK

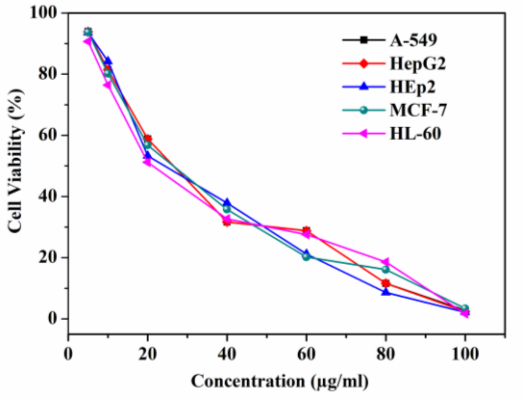

Figure 2: MTT assay measurement on different concentrations of 7- methoxycoumarin against cell viability

Chapter 9 Conclusion

This work thoroughly analyzed the infrared and Raman vibrational spectra of biological and pharmaceutical significant molecules. All the vibrational bands observed in the FTIR and FT-Raman spectra of the molecular systems are assigned to the various modes of vibration. The geometrical optimized parameters of molecules have been performed through DFT calculations and agreed with the available crystal data. The systematic comparison of experimental and theoretical results has shown that the method using scaled DFT functional is the most promising in providing correct vibrational wavenumbers. The calculated HOMO and LUMO energies and NBO studies describe the $\pi \rightarrow \pi^*$, $n \rightarrow \pi$, $n \rightarrow \sigma$ interactions of the molecules, which are responsible for their bioactive properties. The electronic spectra of the molecules are performed which reflects the frontier molecular orbitals. Furthermore, the thermodynamic and total dipole moment properties have been calculated in order to get insight in to the compounds. Furthermore, the Mulliken's charges and reactive sites of MEP surfaces clarify the negative and positive potential spots of molecules. Docking studies explains the binding interactions of the molecules with proteins. ADMET parameters reveal that the selected molecules will be suitable for medical applications with low side effects. These results will help the researchers to design and synthesis new materials and also useful in biochemical, pharmaceutical, electro-optical and many other industries. Further, this versatile tool may be helpful to the scientists who were doing research on the functions of the cells in living organisms and in the other drug activity. All the above results are detailed in chapter 9.

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